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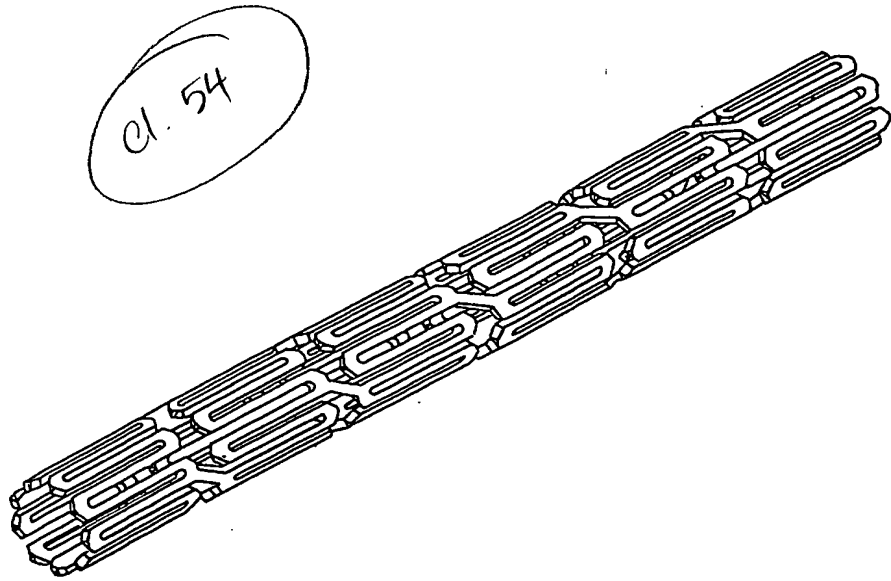
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(54) Title: STENTS HAVING MULTIPLE LAYERS OF BIODEGRADABLE POLYMERIC COMPOSITION



(57) Abstract

An expandable intraluminal stent formed of a material comprised of an inner layer covered by an outer layer, both the inner and outer layers being of biodegradable polymeric composition and exhibiting different time periods of biodegradation is disclosed. The stent is constructed and arranged so that no portion of the inner layer is initially exposed. The stent may also be formed of a framework provided with a first layer of a biodegradable polymer and a second outer layer of a biodegradable polymer over the first layer. The outer layer is further characterized in that it is a surface erodible polymer. Both the inner and outer layers may be impregnated with one or more drugs for drug delivery.

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STENTS HAVING MULTIPLE LAYERS OF BIODEGRADABLE POLYMERIC COMPOSITION

Background of the Invention

5 This invention relates to stents for maintaining the patency of body passages. Additionally, the stents may serve as drug delivery vehicles. The invention has particular application to stenting in blood vessels of the human body and will be described with reference thereto. However, in a broader sense it relates to stenting in any body passage. The invention also has particular reference to stents made of
10 biodegradable composition useful for the treatment and prevention of restenosis and also will find application in dilating and maintaining the patency of various body passages such as ureters and the like.

Summary of the Invention

15 In accordance with a preferred embodiment of this invention a polymeric layered stent is characterized in that it includes a multilayered material comprised of an inner polymer layer and an overlying outer polymer layer. Generally, two forms of stent are contemplated. For one type, any prior art stent may be improved by providing it with a coating layer or layers of polymeric composition.
20 For another type, a stent per se may be provided which is formed of a first inner polymer layer and a second outer or overlying polymer layer, the two polymer layers exhibiting different periods of biodegradation and the outer layer preferably being a surface erodible polymer. Such a stent will exhibit sufficient hoop strength to support the passage wall in which it is implanted and yet be flexible and compliant.

25 Stents according to the invention may be self-expanding or of the type which are expandable from a reduced diameter configuration by an exterior force (as opposed to self-expanding). Both types of stents are well known in the art and need not be described in additional detail herein.

30 Stents according to this invention may be metal stents with one or two polymeric layers thereon, the metal stent providing the basic framework for the device.

Brief Description of the Figures

Figure 1 is an elevational view of one embodiment of a stent according to the present invention.

Figure 2 is a perspective view of another embodiment of a stent in accordance with this invention.

Figure 3 is a cross section taken along line 3-3 of Figure 2.

Figure 4 is a perspective view of yet another embodiment of a stent according to this invention.

Figure 5 is a perspective view of a further embodiment of a stent in accordance with this invention.

Figure 6 is a cross section taken along line 6-6 of Figure 5.

Figure 7 is a view of another stent according to one embodiment of the invention.

Figure 8 is a cross section taken along line 8-8 of Figure 7.

Figures 9 and 10 are exemplary representations of metal stents which may be used with this invention, Figure 10 being fragmentary.

Detailed Description of the Presently Preferred Exemplary Embodiments

Stents to which the present invention relates may be either expandable or self-expanding in form. For example, self-expanding stents are known which are woven or mesh-like in structure, although many other types of self-expanding stents are also known. Such mesh-like stents are in some cases made up of strands which are formed of biodegradable polymeric materials. These stents have memory characteristics and, if distorted in length and/or diameter by external forces, will return or tend to return to a preformed configuration upon the release of external forces. Thus, such a stent is self-expanding when distorted so as to reduce the diameter thereof and subsequently released.

In accordance with the present invention the strands making up such a polymeric stent will be multilayer, i.e., they will be formed of two polymeric composition layers which biodegrade over different periods of time. An inner or core polymeric material is included in the strand as a first layer, which may exhibit a shorter degradation period relative to the outer material, the core material being

enclosed within the outer material, and the outer material exhibiting a longer degradation period relative to the inner material. The outer material is preferably of a surface erodible type polymer.

Such a stent is shown for example in Figure 1 and generally designated
5 10. The stent may be composed of a series of strands arranged in a crossing configuration which may be woven, braided or the like or alternatively it may be formed of a polymeric sheet.

As is typical in the art, the strands of biodegradable material can be deformed so to provide a reduced diameter of the stent which facilitates its delivery to
10 the targeted portion of a vessel or other passageway and once disposed at the target portion the stent can then be allowed to expand to its preformed configuration and larger diameter.

In accordance with one embodiment of the invention, the strands or sheet will be comprised of an inner core polymeric material layer selected to provide
15 strength and support as well as a preselected biodegradation or lifetime. The inner core layer is enveloped or surrounded by an outer layer of material comprised of a second biodegradable polymer selected for its longer biodegradation and the fact that it is preferably a surface erodible polymer. Such an arrangement provides protection of the inner layer material.

20 The multilayer arrangement may be provided in two ways. First, the strands or sheet may be prepared as a multilayer item and then the stent may be made from that item. Secondly, the stent may be first made from the polymeric composition comprising the first or inner layer. Then, after the stent is made, it may be coated with the second or outer polymeric composition by any of the various standard and
25 known coating procedures.

Figure 2 shows a coil stent in which the same arrangement is used, i.e., an inner core layer 12 and an outer covering layer 14 of material having a relatively longer degradation period. The cross-sectional view of Figure 3 shows elements 12 and 14, inner and outer respectively. A strand of the Figure 1 embodiment will be of
30 similar appearance. Of course, the appearance of both types of stent will differ for stents in which the strand is first made of inner material, the stent is then formed and lastly, the stent is coated over-all with the outer material.

Figure 4 shows yet another stent form, a variation of which is shown in Figure 5, the variation comprising apertures in a sheet-like body portion.

Both of these stents may be regarded as being formed from a rolled up flat sheet comprised of a multilayer biodegradable material having an inner layer 16 and an outer biodegradable and preferably erodible material layer 16 similar to the arrangement already described above in connection with Figures 1 and 2. The multilayer sheet is best seen in Figure 6 which is a cross-section of the sheet in Figure 5. The stent may be rolled tightly for delivery and implantation and be self-expandable to the extent that it tends to unroll. Other arrangements are of course possible. For example, if formed as a closed tube, it may simply be expanded by independent expansion means such as a balloon catheter positioned inside the stent as is already known in the art. Of course, the inner sheet may be formed into a stent and then coated, as described above with reference to Figures 1-4.

As already discussed above, a stent formed in accordance with an embodiment of the present invention is formed from biodegradable polymeric materials possessing different relative lifetime periods with respect to their degradation. The particular polymers selected and the thickness of same will determine the rates of biodegradation and the structural characteristics of the stent during degradation should therefore be selected in accordance with the desired degradation and characteristics of the stent.

Materials suitable for use in forming the stents to which the invention relates are such that when fabricated to a desired geometry they will afford the stent sufficient strength and support for the particular intended use. Suitable materials do not produce toxic reactions or act as carcinogens. Suitable materials degrade with the production of physiologically acceptable breakdown products and are preferably absorbed.

The preferred inner or core polymeric materials or underlayment are those such as are set forth in the list immediately below, which is not exhaustive but exemplary only:

30

Poly(L-lactide) (PLLA), Poly(D,L-lactide) (PLA), poly(glycolide) (PGA), poly(L-lactide-co-D,L-lactide) (PLLA/PLA), poly(L-lactide-co-glycolide)

(PLLA/PGA), poly(D,L-lactide-co-glycolide) (PLA/PGA), poly(glycolide-co-trimethylene carbonate) (PGA/PTMC), polydioxanone (PDS), Polycaprolactone (PCL), polyhydroxybutyrate (PHBT), poly(phosphazene) poly(D,L-lactide-co-caprolactone) (PLA/PCL), poly(glycolide-co-caprolactone) (PGA/PCL) and poly(phosphate ester).

Especially preferred materials on this list are PGA and PLLA/PGA.

The outer covering materials will preferably be selected from polyesters, polyamides, polyanhydrides and polyorthoesters. The latter two are more preferred because they are surface erodible types. All of these are exemplary only. Any of the materials listed for the inner layer may be used for the outer layer with appropriate arrangements made for degradation, such as thickness for example.

The outer covering materials are preferably those with long-term biodegradation, and will preferably be selected from the lists included below.

Hydrolysis is the basic reaction for the most biodegradable polymers. The hydrolytic degradation rate can be altered several thousand-fold by changing the chemical structure in the polymer backbone. For example, aliphatic polyanhydrides degrade in a few days while the aromatic polyanhydrides degrade over a period of a few years. Polyorthoester is a slow surface eroding material. In the presence of acid additive, so-called excipient, it has faster degradation rate. In contrast, in the presence of basic substance, it suppresses degradation. So, the aromatic polyanhydride and non-additive polyorthoester will be preferred outer covering materials when longer degradation is desired in the outer layer.

Also, for example, polymers that contain hydrolytically labile linkages in their backbone can hydrolyze by two different mechanisms. These are bulk erosion and surface erosion. In a bulk eroding polymer, the hydrolytic process occurs throughout the matrix of the polymer whereas in surface erosion the hydrolysis is only confined to the outer layer of the polymer. Thus, the latter is especially preferred when longer degradation is desired in the outer layer.

Specific preferred outer materials are, for example:

Poly(ortho esters)

50:50 HD/t-CDM (1,6-Hexanediol-co-trans-Cyclohexanedimethanol) poly(ortho ester)
with 0.2% poly(sebacic anhydride) excipient.

Polyanhydrides

5 poly[bis(p-carboxyphenoxy)propane anhydride] (PCPP)
poly(terephthalic anhydride) (PTA).

If a polyanhydride is selected as the outer material, for example, its thickness can be selected such as to control degradation time or period of say for example two months. The inner core material will for example be PGA at a selected
10 thickness to provide a degradation period of about two weeks, for example. Such a combination will provide a stent which will degrade over a period of three to four months. During the first two months or so of implantation the stent will be covered by tissue. Once tissue grows over the stent the stent will then be degraded with respect to the material within the tissue.

15 Multilayered biodegradable polymer material with one short-term inner layer and one long-term outer layer for demonstrating the application of the concept to stent usage is described as follows. The inner layer made of PGA or PLA is first dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFP) or in tetrahydrofuran (THF) at a concentration of 20% (wt/wt), then poured into a glass dish to cast a thin membrane.
20 The inner layer may have a thickness from 0.05 - 0.50 mm, preferably 0.10 - 0.25 mm. The thickness is controlled by the volume or the concentration of polymer solution used. The polymer solution in the glass dish should be dried at room temperature and in a hood with good ventilation.

The dried polymer membrane is cut to a strip for adding the outer layer
25 polymer. The dimension depends on the final stent design. A simple configuration may be in spiral coil form for using as coronary implant, the inner strip being 0.10 - 0.25 mm thick, 1.0 - 2.0 mm width and 30 - 80 mm length.

The second material used for the outer layer may be chosen from the long-term biodegradable materials such as polycaprolactone (PCL), (PCPP) or (PTA).
30 It may be dissolved in THF at a concentration of 5-20% (wt/wt). Adding the outer layer onto inner layer may be carried out by spraying or painting. The outer layer thickness may be about 0.05 - 0.50 mm, preferably 0.10 - 0.25 mm.

The finished multilayer strip is dried completely, then formed in a metal die under heating to a shape of a spiral coil. The temperature used is lower than the melting point of both inner and outer layer materials. The final product may have a diameter of about 4.5 mm and 18 mm length and five spiral cycles.

5 The outer layer may be used as a drug-delivery system to prevent restenosis or for other treatment. The drugs may include radiochemicals to irradiate and prohibit tissue growth. Angioplasty and stent deployment may cause injury of the endothelial cell layer of blood vessels, causing smooth muscle cell proliferation, leading to restenosis. To control smooth muscle cell growth endothelialization of cells
10 on the inner wall surface of vessels will prevent or prohibit the smooth muscle growth. To stimulate endothelialization without provoking smooth muscle cell proliferation human growth factors may be included in the outer layer and delivered. Growth factors include VEGF (Vascular Endothelial Growth Factor), TGF-beta (Transforming Growth Factor-beta), IGF (Insulin - like Growth Factor), PDGF
15 (Platelet - derived Growth Factor), FGF (Fibroblast Growth Factor), etc. These growth factors are dispersed in the matrix of outer polymer body of the stent. All such materials are referred to herein generally as "drugs".

For carrying drugs, a gel-like material may be used. It may be applied over the top layer/outer layer of polymeric material or directly to a metal stent or used
20 as a second outer layer. There are two ways to apply drugs to such materials. The first way is to mix the drug with the materials, then coat the mixture onto a stent. They can be cast as film or sheet with drug together, then laminated to the core stent. A second way is to coat or laminate polymer with the core stent without the drug. The stent device is made, then sterilized. Due to their gel-like nature, the stent can
25 then be inserted into a drug solution. The drug will be absorbed into/onto the gel. The stent can then be delivered into the body (dried or not dried). The drug will be released.

In another embodiment of the invention the inner polymer layer may have a longer degradation time than the outer layer to provide an initial short burst of
30 drugs then a slower long term drug release from the inner layer may be a block copolymer such as PGA/PLA, PEO/PLA (Polyethylene oxide / PLA) or the like containing a drug such as Taxol. The outer layer may be PEO containing Taxol.

Preferred gel-like materials are polyethylene oxide, polyvinyl pyrrolidone, polyacrylates, and their blends or copolymers or lightly crosslinked forms. Polyethylene glycol block copolymer with polylactides or other polyesters are examples. Hydrophilic polyurethane, poly(maleic anhydride-alt-ethylene) and their derivatives are examples. Other materials are polysaccharides and their derivatives. There are also sodium alginate, karaya gum, gelatin, guar gum, agar, algin, carrageenans, pectin, locust bean gums, xanthan, starch-based gums, hydroxyalkyl and ethyl ethers of cellulose, sodium carboxymethylcellulose. Some of the materials will be heated, then cooled, then a gel is formed. Some of the are food gels. Some of them are bioadhesives.

Any drugs may be used, singly or in combination. For example, the drugs can be an anticoagulant, e.g. D-Phe-ProArg chloromethyl ketone. An RGD (Arginine-Glycine-Aspartic Acid) peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, antibodies, aspirin, prostaglandin inhibitors, platelet inhibitors, or antiplatelet peptide. The drug can be an inhibitor of vascular cell growth, DNA, RNA, cholesterol-lowering agents, vasodilating agents. The drug can be any drug such as Taxol, 5-Fluorouracil, Beta-Estradiol or any combination of them.

Since there are many drugs and many polymers, the stent can have multiple layers of different polymers with the same or different drugs. For example, the stent can have two layers of the same polymer with one layer with drug and another layer without drugs. The stent can have two layers of the same polymer with two different drugs.

In particular, various combinations of a cyclinase inhibitor identified as p21 and the vascular endothelial growth factor identified as VEGF, an endothelial nitrogen, may preferably be included in and dispensed from the outer polymer layer of a stent.

Incorporation of drugs and growth factors into a polymer layer can also be performed by several other methods, including the solvent method, melting method, soaking method and spaying method. If both polymer and drug have a co-solvent, a solution case will be an easy way to provide the polymer matrix loaded with the drug or growth factor. If the polymer can be melted at low temperature and the

drug or growth factor tolerates heating, a melting method can be used to mix the drug or growth factor into the polymer matrix. Also, a polymer-drug solution or suspension solution can be used for coating to provide a layer containing the drug or growth factor.

5 Another embodiment of the invention contemplates the provision on any stent per se taken from the prior art, such as a metal stent, with a first or under coating layer of a polymer and a second or outer coating layer of a polymer on at least the outer surface of the stent covering the first layer, the coating layers exhibiting different periods of degradation. Again, the outer layer may include a drug or drugs
10 or mixtures thereof.

 Figures 7 and 8 show such a stent which is of metal such as stainless steel or any other metal or material as is known in the art. The basic metal stent structure 22 carries a multilayer coating as shown in Figure 8 of a polymer undercoat layer 24 and an outer polymer layer 26. Layers 24 and 26 may be included only on
15 the outer surface of the stent or on both inner and outer surfaces as shown in Figure 8.

 Placing the polymer layers onto a metal stent can be done by a coating method, both inner and outer layer polymers are pre-dissolved into suitable solvent, by dipping or spraying a first solution of the first polymer onto the surface of metal stent. After drying then a second solution of the second polymer can be placed again,
20 to form the multiple polymer layers.

 The first or under coating layer may be selected from the list of preferred materials immediately below, which is not exhaustive:

25 Poly(L-lactide) (PLLA), Poly(D,L-lactide) (PLA), poly(glycolide (PGA), poly(L-lactide-co-D,L-lactide) (PLLA/PLA), poly(L-lactide-co-glycolide) (PLLA/PGA), poly(D,L-lactide-co-glycolide) (PLA/PGA), poly(glycolide-co-trimethylene carbonate) (PGA/PTMC), polydioxanone (PDS), Polycaprolactone (PCL), polyhydroxybutyrate (PHBT), poly(phosphazene) poly(D,L-lactide-co-caprolactone) (PLA/PCL), poly(glycolide-co-
30 caprolactone) (PGA/PCL) and poly(phosphate ester).

Preferred materials on this list are PGA and PLLA/PGA.

The preferred second or outer coating materials may be selected from the list provided herein below, which is not exhaustive:

Polycaprolactone (PCL), polyhydroxybutyrate (PHBT), polyanhydrides (PAN), poly(ortho esters), poly(phosphazene) and poly(phosphate ester).

5 Most preferably the polyanhydrides and polyorthoesters will be utilized.

As before, if a polyanhydride is selected as the outer layer material its thickness can be selected such as to control degradation time or period of say for example two months. The under coating material may for example be PGA at a
10 selected thickness to provide a degradation period of about two weeks, for example.

Multilayered biodegradable material may be placed on a metal stent by coating techniques the inner layer may be short-term and the outer layer may be long-term polymer, or the inner layer may be long-term and outer layer short-term polymer. Both inner and outer layers may include drugs.

15 In the long-term inner layer and short-term outer layer design, PGA or PLA may be dissolved in chloroform at a concentration of 20% (wt/wt), the metal stent is dipped in the polymer solution, then removed. After drying at room temperature, a thin layer of PGA or PLA may be coated on the metal strut. The coating thickness may be about 0.001 - 0.2 mm, preferably 0.01 - 0.10 mm. It may
20 be adjusted by the dipping times and the concentration of the polymer solution. One, two or more drugs may be included in the polymer solution and cast into the inner layer with the polymer.

After finishing the inner layer, a second polymer solution may be placed onto the inner layer by painting or spray methods PEO may be selected as the
25 outer layer and dissolved into chloroform with 2% (wt/wt) concentration. The thickness of the outer layer may be 0.001 - 0.50 mm, preferably 0.01 - 0.20 mm. One, two or more drugs may be added into this PEO solution to cast with the outer layer also.

30 Again, the outer coating layer may include a radiochemical or drug(s) as described hereinabove with reference to other embodiments of the invention.

Another embodiment of the invention includes a metal stent such as the preferred types shown in Figure 9 and Figure 10, for example, with a single

polymeric layer or coating thereon. For example, a block copolymer such as polyethylene glycol with polylactides (PEO/PLA) or other copolymers with polyesters (PE), for example, (PEO/PE) such as PGA, PLLA, or PCL may be used. In such a polymer, the relative amounts of the copolymers may be adjusted to affect the release
5 time of the drug(s). By adjusting the amount and/or chain length of the PEO the release time can be shortened. By adjusting the amount or chain length of the PLA the release time can be lengthened. Other copolymers may be used as well.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiments, it is to be
10 understood that the invention is not to be limited to the disclosed embodiments but, on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

What is claimed is as follows:

1. A stent formed of a framework, the framework provided with a first layer of a biodegradable polymer and a second outer layer of a biodegradable polymer over the first layer, the layers exhibiting different time periods of biodegradation, the outer layer and the framework completely surrounding the first layer, the stent having apertures therethrough, the apertures distributed about the stent.
2. The stent of claim 1 wherein the outer layer is further characterized in that it is a surface erodible polymer.
3. The stent of claim 1 wherein the outer layer is comprised of a material selected from the group consisting of polyamides, polyorthoesters and polyanhydrides.
4. The stent of claim 1 wherein the outer layer is a gel-like polymer.
5. The stent of claim 1 wherein the outer layer exhibits a longer-biodegradation period than the inner layer.
6. The stent of claim 1 wherein the outer layer exhibits a shorter biodegradation period than the inner layer.
7. The stent of claim 1 wherein the first layer is comprised of a material selected from the group consisting of PGA and PLLA/PGA.
8. The stent of claim 1 including a drug in at least one of the first layer and the outer layer.
9. The stent of claim 8 wherein the drug is selected from the group consisting of p21, VEGF, Taxol, Beta-Estradiol and combinations thereof.
10. The stent of claim 1 wherein the framework carrying the polymer layers is metal.
11. The stent of claim 1 wherein the inner layer is a block copolymer.
12. The stent of claim 11 wherein the block copolymer is PEO/PLA.
13. The stent of claim 1 wherein the outer layer is PEO.
14. An expandable intraluminal stent comprising a main body portion having a first end, a second end and a flow passage defined therethrough, the main body portion being sized for intraluminal placement within a body passage and subsequent expansion for implantation, the main body portion being further characterized in that it is formed of a material comprised of an inner layer covered by one or more outer layers, the inner and outer layers being of biodegradable polymeric composition and exhibiting different time periods of biodegradation, the stent constructed and arranged so that no portion of the inner layer is initially exposed.

inner core
slower than
outer

15. The stent of claim 14 wherein at least one of the inner layer and the one or more outer layers further comprises a drug.

5

Fig.1

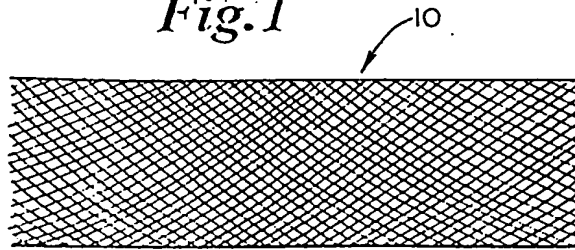


Fig.2

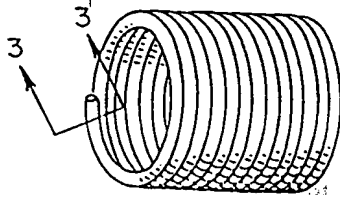


Fig.3

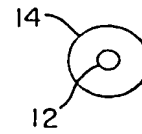


Fig.4

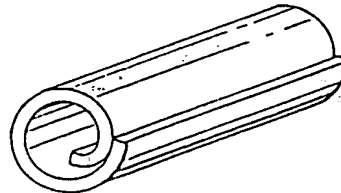


Fig.5

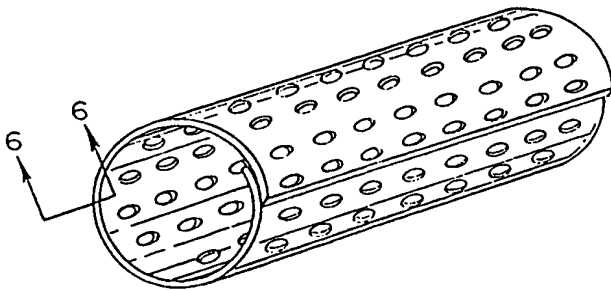


Fig.6

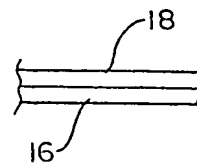


Fig. 7

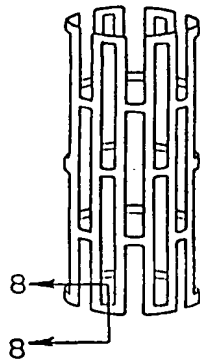
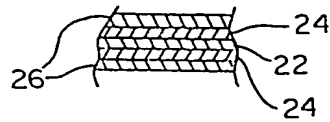


Fig. 8



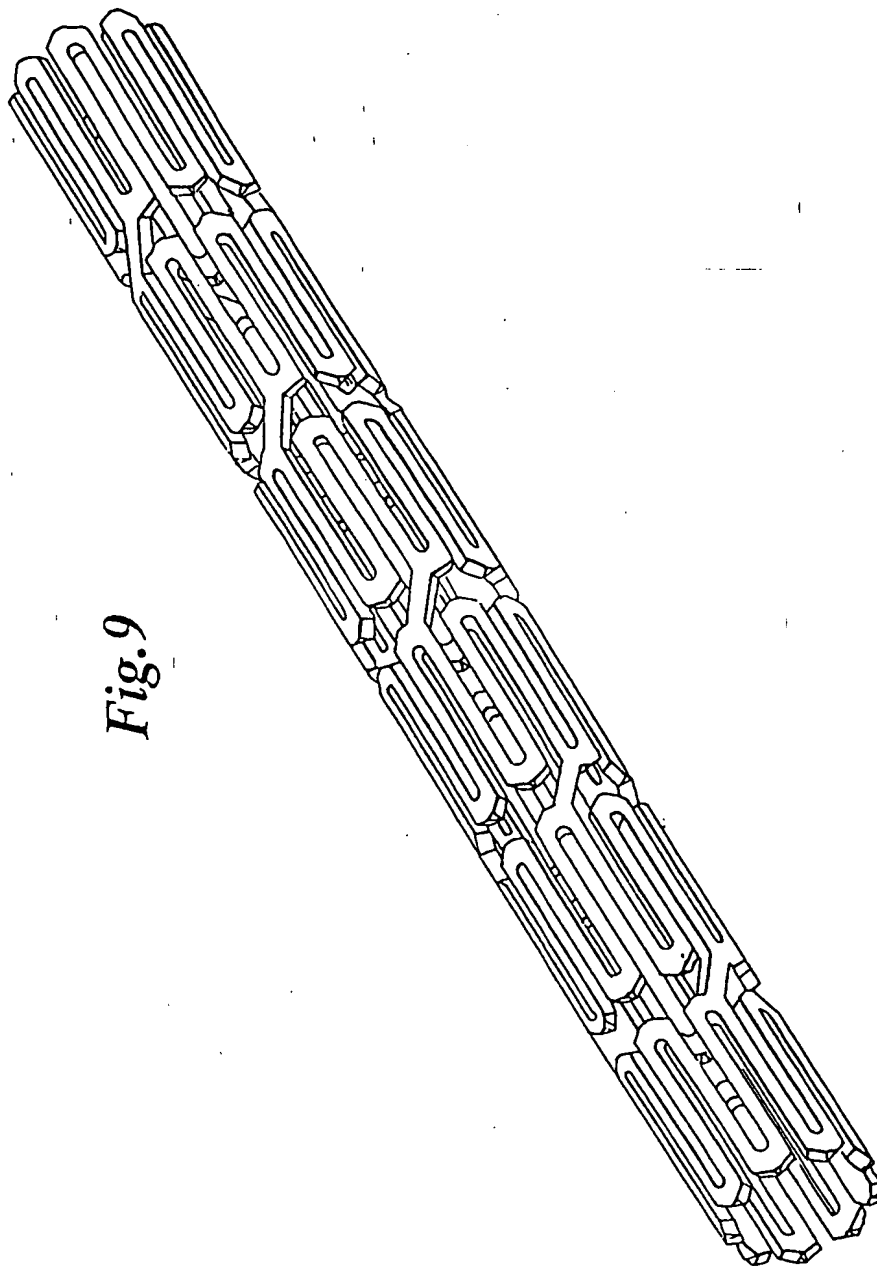
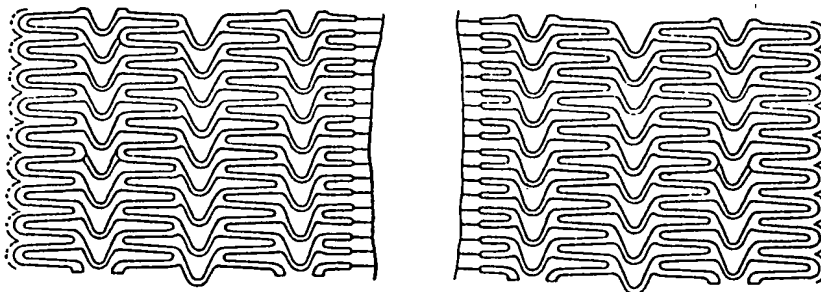


Fig. 9

Fig.10



INTERNATIONAL SEARCH REPORT

National Application No
PCT/US 98/12228

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 06792 A (SCIMED LIFE SYSTEMS INC.) 15 April 1993	1,5-8, 14,15
Y	see the whole document -----	2,3,9,10
Y	WO 90 09783 A (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 7 September 1990 see the whole document -----	2,3,9
Y	WO 96 25176 A (NEORX CORPORATION) 22 August 1996 see page 6, line 3 - line 19 -----	10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 14 September 1998	Date of mailing of the international search report 21/09/1998
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Smith, C
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/12228

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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